NKX3-1 is required for induced pluripotent stem cell reprogramming and can replace OCT4 in mouse and human iPSC induction.

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Public Summary:
Reprogramming somatic cells to induced pluripotent stem cells (iPSCs) is now routinely accomplished by overexpression of the four Yamanaka factors (OCT4, SOX2, KLF4, MYC (or OSKM))(1). These iPSCs can be derived from patients' somatic cells and differentiated toward diverse fates, serving as a resource for basic and translational research. However, mechanistic insights into regulators and pathways that initiate the pluripotency network remain to be resolved. In particular, naturally occurring molecules that activate endogenous OCT4 and replace exogenous OCT4 in human iPSC reprogramming have yet to be found. Using a heterokaryon reprogramming system we identified NKX3-1 as an early and transiently expressed homeobox transcription factor. Following knockdown of NKX3-1, iPSC reprogramming is abrogated. NKX3-1 functions downstream of the IL-6-STAT3 regulatory network to activate endogenous OCT4. Importantly, NKX3-1 substitutes for exogenous OCT4 to reprogram both mouse and human fibroblasts at comparable efficiencies and generate fully pluripotent stem cells. Our findings establish an essential role for NKX3-1, a prostate-specific tumour suppressor, in iPSC reprogramming.

Scientific Abstract:
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